Chrial salts of pantoprazole and the process of preparation thereof

Field of the invention:

The present invention relates to an antiulcer drug, the laveno(-) and dextral(+) enantiomer salts of (±)5-difluromethoxy-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole, that is the S(-) potassium pantoprazole, S(-) sodium pantoprazole, S(-) magnesium pantoprazole, S(-) calcium pantoprazole, S(-) zinc pantoprazole and R(+) potassium pantoprazole, R(+) sodium pantoprazole, R(+) magnesium pantoprazole, R(+) calcium pantoprazole, R(+) zinc pantoprazole, in other words, the present invention relates to the chiral salts of pantoprazole and a process for the preparation thereof.

Prior art:

The compound with the general name of pantoprazole has a chemical name as (±)5-difluromethoxy-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole, the neutral style and sodium salt thereof are described in EP0166287, pantoprazole is an inhibitor of H^+, K^+-ATP enzyme (proton pump), which can effectively inhibit the secretion of gastric acid, and is used in the treatment of diseases related to gastric acid secrection disorder, such as gastric ulcer, duodenal ulcer, reflux esophagitis, Zollinger-Ellison syndrome etc.

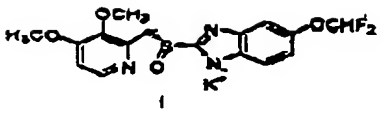
The sulfur atom in the molecule of pantoprazole is a stereoisomeric center. Therefore, pantoprazole is a recemic mixture of laveno(-) and dextral(+), i.e., S(-) and R(+) type enantiomers, and the salts thereof also have the corresponding configurations. Likewise, the chiral pantoprazole salts of the present invention are an inhibitor of proton pump and are used in the treatment of diseases related to gastric acid secrection disorder, such as gastric ulcer, duodenal ulcer, reflux esophagitis, Zollinger-Ellison syndrome etc. A preliminary pharmacological test result shows that the salts of S(-)pantoprazole have better effect than the racemate of pantoprazole in inhibiting the secretion of gastric acid.

The process for the preparation of single enantiomer of pantoprazole is described in WO92/08716 and WO96/27989.

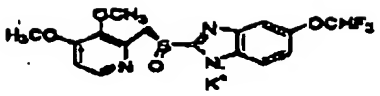
The method used in WO92/08716 is resolution, while the method used in WO96/27989 is chrial oxidation.

Discription of the invention:

The S(-)pantoprazole and R(+)pantoprazole in the present invention are obtained by chiral oxidation in the presence of Sharpless reagent with chloroform or acetonitrile as solvent; S(-)pantoprazole or R(+)pantoprazole is reacted with potassium hydroxide, potassium carbonate, potassium methoxide, potassium ethoxide, and potassium isopropoxide respectively to obtain S(-) potassium pantoprazole (I) or R(+) potassium pantoprazole(II):



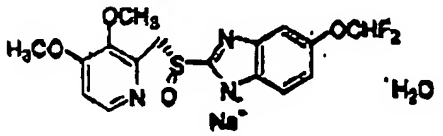
I



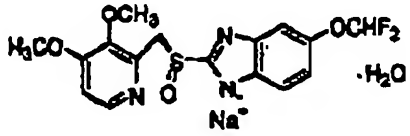
II

S(-)pantoprazole or R(+)pantoprazole is reacted with sodium hydroxide, sodium methoxide, sodium ethoxide and sodium isopropoxide respectively to obtain S(-) sodium pantoprazole(III) or R(+) sodium pantoprazole(IV):

S(-)pantoprazole or R(+)pantoprazole is reacted with magnesium lower alkoxide, such as magnesium methoxide or magnesium ethoxide respectively to

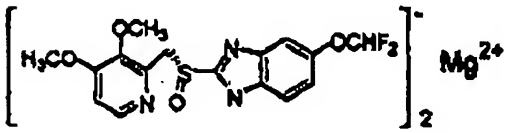


III

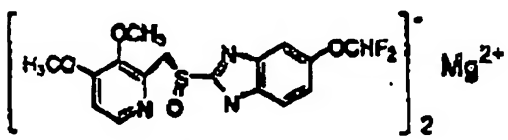


IV

obtain S(-) magnesium pantoprazole(V) or R(+) magnesium pantoprazole(VI), or S(-) potassium pantoprazole (I) and S(-) sodium pantoprazole(III) or R(+) potassium pantoprazole(II) and R(+) sodium pantoprazole(IV) is reacted with a magnesium source such as magnesium chloride, magnesium sulfate, or magnesium acetate etc. to obtain S(-) magnesium pantoprazole(V) or R(+) magnesium pantoprazole(VI):



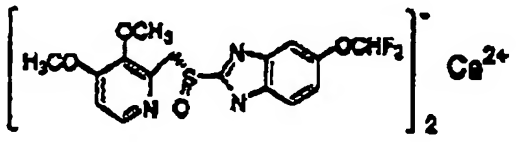
V



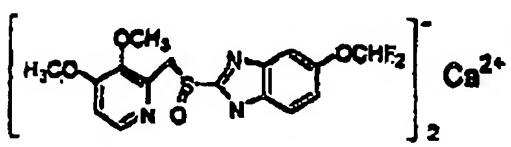
VI

S(-) Potassium pantoprazole (I) and S(-) sodium pantoprazole(III) or R(+) potassium pantoprazole(II) and R(+) sodium pantoprazole(IV) were reacted with a calcium source such as calcium chloride, calcium acetate etc. to obtain S(-) calcium pantoprazole(VII) or R(+) calcium pantoprazole(VIII);

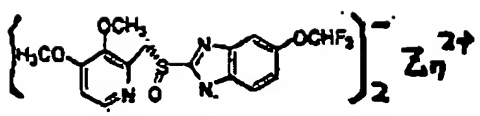
S(-) Potassium pantoprazole (I) and S(-) sodium pantoprazole(III) or R(+) potassium pantoprazole(II) and R(+) sodium pantoprazole(IV) were reacted with a zinc source such as zinc chloride, zinc acetate etc. to obtain S(-) zinc pantoprazole(IX) or R(+) zinc pantoprazole(X):



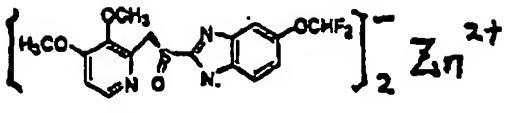
VII



VIII



IX



X

The solvent used in the reaction is methanol, ethanol, isopropanol or acetone; the temperature in the reaction is from 0℃ to the boiling point of the solvent used, 20-40℃ is preferred.

The advantages of present invention are: the present invention provides new salt structures of pantoprazole, which can be used as inhibitor of proton pump in the treatment of diseases related to gastric acid secrection disorder, furthermore, it is promising to develop new combination of drugs acceptable in treatment from the present invention. The process of preparation in the present invention is simple, easily operable, and suitable for industrial production.

Examples:

Example 1:

Synthesis of S(-) Potassium pantoprazole (I)

3.83g(10mmol) of S(-)pantoprazole were mixed with 40ml of acetone at 35℃ and a solution of 0.68g(10mmol) of potassium hydroxide in 3ml of methanol was added dropwise, after 3 hours of stirring , the mixture was cooled to 5℃ and filtrated by suction, the product collected was dried in vacuo at 80℃. 3.6g of S(-) Potassium pantoprazole were obtained as white crystal, yield: 82%.

Example 2:

Synthesis of R(+) Potassium pantoprazole (II)

3.83g(10mmol) of R(+)pantoprazole were mixed with 40ml of acetone at 35℃ and a solution of 0.68g(10mmol) of potassium hydroxide in 3ml of methanol was added dropwise, after 3 hours of stirring , the mixture was cooled to 5℃ and filtrated by suction, the product collected was dried in vacuo at 80℃. 3.5g of R(+) Potassium pantoprazole were obtained as white crystal, yield: 80%.

Example 3:

Synthesis of S(-) sodium pantoprazole(III)

38.3g(0.1mol) of S(-)pantoprazole were mixed with 400ml of acetone at 35℃ and a solution of 4.0g(0.1mol) of sodium hydroxide in 10ml of water was added dropwise, after 3 hours of stirring , the mixture was cooled to 5℃ and filtrated by suction, the product collected was dried in vacuo at 80℃. 36g of S(-) sodium pantoprazole(containing one molecular of water) were obtained as white crystal, yield: 85%. $[\alpha]_D^{20}$-124.0(acetonitrile:methanol=1:1).

Example 4:

Synthesis of R(+) sodium pantoprazole(IV)

38.3g(0.1mol) of R(+) pantoprazole were mixed with 400ml of acetone at 35℃ and a solution of 4.0g(0.1mol) of sodium hydroxide in 10ml of water was added dropwise, after 3 hours of stirring , the mixture was cooled to 5℃ and filtrated by suction, the product collected was dried in vacuo at 80℃. 36.2g of R(+) sodium pantoprazole(containing one molecular of water) were obtained as white crystal, yield: 86%, $[\alpha]_D^{20}$+121.6(acetonitrile:methanol=1:1).

Example 5:

Synthesis of S(-) magnesium pantoprazole(V)

0.24g(0.01mol) of magnesium was added to 25ml of methanol, after being refluxed for 90 min with stirring, the mixture was cooled to room temperature, 7.7g(0.02mol) of S(-)pantoprazole were added and reacted for 2 hours, thereafter, the mixture was filtered to remove the insoluble substance ,75ml of water was added into the filtration slowly before another 3 hours of stirring, then the mixture was cooled to 5℃, filtrated by suction . the filter cake was washed with 60ml×3 of water, dried in vacuo to obtain 7.0g of S(-) magnesium pantoprazole, yield: 88%. m.p.:168-170℃.

Example 6:

Synthesis of R(+) magnesium pantoprazole(VI)

0.24g(0.01mol) of magnesium was added to 25ml of methanol, after being refluxed for 90 min with stirring, the mixture was cooled to room temperature, 7.7g(0.02mol) of R(+) pantoprazole were added and reacted for 2 hours, thereafter, the mixture was filtered to remove the insoluble substance, 75ml of water was added into the filtration slowly before another 3 hours of stirring, then the mixture was cooled to 5℃, filtrated by suction . The filter cake was washed with 60ml×3 of water, dried in vacuo to obtain 6.8g of R(+) magnesium pantoprazole, yield: 86%. m.p.:167-169℃.

Example 7:

Synthesis of S(-) magnesium pantoprazole(V)

42.3g (0.1mol)of S(-) sodium pantoprazole monohydrate were dissolved into 150ml of water, a solution of 10.8g(0.05mol) magnesium acetate in 30ml of water was added with stirring, after being stirred for 60min, the mixture was cooled to 10℃, filtrated by suction, the filter cake was washed with water, and dried, 35.5g of S(-) magnesium pantoprazole were obtained as white powder, yield: 90%.

Example 8:

Synthesis of R(+) magnesium pantoprazole(VI)

42.3g (0.1mol)of R(+)sodium pantoprazole monohydrate were dissolved into 150ml of water, a solution of 10.8g(0.05mol) magnesium acetate in 30ml of water was added , after being stirred for 60min, the mixture was cooled to 10 ℃, filtrated by suction, the filter cake was washed with water, and dried, 35.6g of R(+)magnesium pantoprazole were obtained as white powder, yield: 90%.

Example 9:

Synthesis of S(-) calcium pantoprazole(Ⅶ)

4.23g(10mmol) of S(-) sodium pantoprazole monohydrate were dissolved into 150ml of water, a solution of 0.56g(5mmol) calcium chloride in 5ml of water was added with stirring, afer being stirred for 60min, the mixture was cooled to 10 ℃, filtrated by suction, the filter cake was washed with water to the extent that there is no chloride ion in the filtration, and dried, 3.6g of S(-) calcium pantoprazole were obtained as white powder, yield: 85%.

Example 10:

Synthesis of R(+) calcium pantoprazole(Ⅷ)

4.23g (10mmol) of R(+) sodium pantoprazole monohydrate were dissolved into 150ml of water, a solution of 0.56g(5mmol) calcium chloride in 5ml of water was added with stirring, afer being stirred for 60min, the mixture was cooled to 10 ℃, filtrated by suction, the filter cake was washed with water to the extent that there is no chloride ion in the filtration, and dried, 3.4g of R(+) calcium pantoprazole were obtained as white powder, yield: 81%.

Example 11:

Synthesis of S(-) zinc pantoprazole(Ⅸ)

2.1g (5mmol)of S(-) sodium pantoprazole monohydrate were dissolved into 150ml of water, a solution of 0.62g(5mmol) zinc acetate in 5ml of water was added with stirring, after being stirred for 60min, the mixture was cooled to 10 ℃, filtrated by suction, the filter cake was washed with water , and dried, 2.1g of S(-) zinc pantoprazole were obtained as white powder, yield: 90%.

Example 12:

Synthesis of R(+) zinc pantoprazole(Ⅹ)

2.1g (5mmol)of R(+) sodium pantoprazole monohydrate were dissolved into 150ml of water, a solution of 0.62g(5mmol) zinc acetate in 5ml of water was added with stirring, afer being stirred for 60min, the mixture was cooled to 10 ℃, filtrated by suction, the filter cake was washed with water , and dried, 2.0g of R(+) zinc pantoprazole were obtained as white powder, yield: 88%.

Example 13:

Synthesis of S(-) pantoprazole

36.7g (0.1mol)of 5-difluromethoxy-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole were dissolved into 400ml of chloroform, 0.1ml (5.8 μ mol) of water, 4.4ml(0.02mol) of (-)diethyl tartrate and 3ml(0.01mol) of titanium isopropoxide(Ⅳ) were added into the mixture above, after being refluxed for 60min, 3ml(0.03mol) of triethylamine, 23ml(0.1mol) of cumene peroxide(70%) was added at room temprature therein, stirred for 5 hours, chloroform was recovered by concentrating the mixture under reduced pressure, 250ml of acetonitrile was added

into the residue, which was cooled, filtrated by suction and dried to obtain 27g of S(-) pantoprazole, yield: 70%, m.p.:144-145 ℃ (decomposed), $[\alpha]_D^{20}$-143(acetonitrile:methanol=1:1).

Example 14:

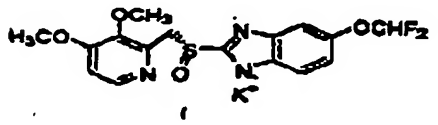
Synthesis of R(+)pantoprazole

36.7g(0.1mol) of 5-difluromethoxy-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole were dissolved into 400ml of chloroform, 0.1ml (5.8 μ mol) of water, 4.4ml(0.02mol) of (+)diethyl tartrate and 3ml(0.01mol) of titanium isopropoxide(IV) were added into the mixture above, after being refluxed for 60min, 3ml(0.03mol) of triethylamine, 23ml(0.1mol) of cumene peroxide(70%) was added at room temprature therein, stirred for 5 hours, chloroform was recovered by concentrating the mixture under reduced pressure, 250ml of acetonitrile was added into the residue, which was cooled, filtrated by suction and dried to obtain 26.5g of R(+)pantoprazole, yield: 68%, m.p.:142-144 ℃ (decomposed), $[\alpha]_D^{20}$+147(acetonitrile:methanol=1:1).

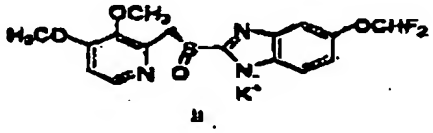
Claims

1. A chrial salt of pantoprazole, which is characterized in the following structure:

a. the chrial potassium pantoprazole, wherein the structures of S(-) potassium pantoprazole (I) and R(+) potassium pantoprazole(II) are as follows:



I



II

b. the chrial sodium pantoprazole, wherein the structures of S(-) sodium pantoprazole(III) and R(+) sodium pantoprazole(IV) are as follows:

c. the chrial magnesium pantoprazole, wherein the structures of S(-) magnesium pantoprazole(V) and R(+) magnesium pantoprazole(VI) are as follows:

III

IV

V

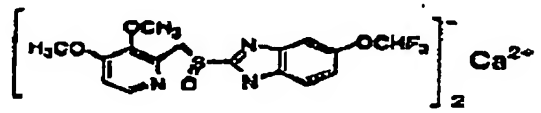
VI

d. the chrial calcium pantoprazole, wherein the structures of S(-) calcium pantoprazole(VII) and R(+) calcium pantoprazole(VIII) are as follows:

e. the chrial zinc pantoprazole, wherein the structures of S(-) zinc pantoprazole(IX) and R(+) zinc pantoprazole(X) are as follows:

2. A process for the preparation of chrial salts of pantoprazole according to

VII



VIII

IX

X

claim 1, which is characterized in that:

The S(-)pantoprazole or R(+)pantoprazole is reacted with potassium hydroxide, potassium carbonate, potassium methoxide, potassium ethoxide or potassium isopropoxide respectively to obtain S(-) potassium pantoprazole (I) or R(+) potassium pantoprazole(II), the solvent used in the reaction is water, acetone,

methanol, ethanol or isopropanol, the temprature in the reaction is from 0℃to the boiling point of the solvent used, 20-40℃ is preferred.

3. A process for the preparation of chrial salts of pantoprazole according to claim 1, which is characterized in that:

The S(-)pantoprazole or R(+)pantoprazole is reacted with sodium hydroxide, sodium methoxide, sodium ethoxide and sodium isopropoxide respectively to obtain S(-) sodium pantoprazole(III) or R(+) sodium pantoprazole(IV), the solvent used in the reaction is water, acetone, methanol, ethanol or isopropanol, the temprature in the reaction is from 0℃to the boiling point of the solvent used, 20-40℃ is preferred.

4. A process for the preparation of chrial salts of pantoprazole according to claim 1, which is characterized in that:

a) The S(-)pantoprazole or R(+)pantoprazole is reacted with magnesium lower alkoxide, such as magnesium methoxide or magnesium ethoxide respectively to obtain S(-) magnesium pantoprazole(V) or R(+) magnesium pantoprazole(VI), the solvent used in the reaction is methanol, ethanol, isopropanol or acetone, the temprature in the reaction is from 0℃ to the boiling point of the solvent used, 20-40 ℃ is preferred,

b) S(-) Potassium pantoprazole (I) and S(-) sodium pantoprazole(III) or R(+) potassium pantoprazole(II) and R(+) sodium pantoprazole(IV) are reacted with a magnesium source such as magnesium chloride, magnesium sulfate, or magnesium acetate etc. to obtain S(-) magnesium pantoprazole(V) or R(+) magnesium pantoprazole(VI), the solvent used in the reaction is water, methanol, ethanol or isopropanol, the temprature in the reaction is from 0℃ to the boiling point of the solvent used, 20-40℃ is preferred.

5. A process for the preparation of chrial salts of pantoprazole according to claim 1, which is characterized in that:

S(-) Potassium pantoprazole (I) and S(-) sodium pantoprazole(III) or R(+) potassium pantoprazole(II) and R(+) sodium pantoprazole(IV) are reacted with a calcium source such as calcium chloride, calcium acetate etc. to obtain S(-) calcium pantoprazole(VII) and R(+) calcium pantoprazole(VIII), the solvent used in the reaction is water, methanol, ethanol, isopropanol or acetone, the temprature in the reaction is from 0℃ to the boiling point of the solvent used, 20-40℃ is preferred.

6. A process for the preparation of chrial salts of pantoprazole according to claim 1, which is characterized in that:

S(-) Potassium pantoprazole (I) and S(-) sodium pantoprazole(III) or R(+) potassium pantoprazole(II) and R(+) sodium pantoprazole(IV) are reacted with a zinc source such as zinc chloride, zinc acetate etc. to obtain S(-) zinc pantoprazole(IX) and R(+) zinc pantoprazole(X), the solvent used in the reaction is water, methanol, ethanol, isopropanol or acetone, the temprature in the reaction is from 0℃ to the boiling point of the solvent used, 20-40℃ is preferred.

7. A chiral salt of pantoprazole according to claim 2, 3, or 4, which is characterized in that: a new process for the preparation of S(-)pantoprazole and R(+)pantoprazole in the preparation thereof is used, in which chloroform or acetonitrile is used as solvent.

8. a chiral salt of pantoprazole according to claim 1, which is characterized in that: it can be used in combination with other drugs acceptable in treatment for the preparation of medicaments treating gastric ulcer, duodenal ulcer, reflux esophagitis and Zollinger-Ellison syndrome.

Abstract:

The present invention relates to an antiulcer drug, the laveno(-) and dextral(+) enantiomer salts of (±)5-difluromethoxy-[[(3,4-dimethoxy-2-pyridyl)methyl]sulfinyl]-1H-benzimidazole, that is the S(-) potassium pantoprazole, S(-) sodium pantoprazole, S(-) magnesium pantoprazole, S(-) calcium pantoprazole, S(-) zinc pantoprazole and R(+) potassium pantoprazole, R(+) sodium pantoprazole, R(+) magnesium pantoprazole, R(+) calcium pantoprazole, R(+) zinc pantoprazole. This invention also provides a new process for the preparation of S(-)pantoprazole and R(+)pantoprazole, which is obtained by chiral oxidation in the presence of Sharpless reagent with chloroform or acetonitrile as solvent, followed by the reaction with potassium hydroxide or potassium carbonate etc. It's promising to develop new drugs useful in the treatment of diseases related to gastric acid secretion disorder from this invention.

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[54]发明名称 手性泮托拉唑盐及其制备方法

[57]摘要

本发明涉及抗消化溃疡药物(±)5-二氟甲氧基-[[(3,4-二甲氧基-2-吡啶基)甲基]亚磺酰基]-1H-苯并咪唑的左旋(-)和右旋(+)对映体的盐,即S(-)泮托拉唑钾、钠、镁、钙、锌盐R(+)泮托拉唑钾、钠、镁、钙、锌盐。本发明还提供S(-)泮托拉唑和R(+)泮托拉唑的一种新制备方法,以氯仿或乙腈作溶剂,在Sharpless试剂存在下进行手性氧化制得,在与氢氧化钾、碳酸钾等反应得到。本发明可望开发出治疗与胃酸分泌紊乱有关疾病的新药。

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不溶物，缓慢加入水 75mL 继续搅拌 3 小时，冷却至 5℃，抽滤，用 60mL 水分三次洗涤，经减压干燥得 R（+）泮托拉唑镁 6.8g，收率：86%。mp: 167~169℃。

实施例 7

S（-）泮托拉唑镁（V）的合成

将 42.3g（0.1mol）的 S（-）泮托拉唑钠一水合物溶于 150mL 水中，搅拌下加入 10.8g（0.05mol）乙酸镁溶于 30mL 水的溶液，搅拌 60 分钟，冷却至 10℃，抽滤，水洗，干燥，得白色粉末 S（-）泮托拉唑镁 35.5g，收率：90%。

实施例 8

R（+）泮托拉唑镁（VI）的合成

将 42.3g（0.1mol）的 R（+）泮托拉唑钠一水合物溶于 150mL 水中，加入 10.8g（0.05mol）乙酸镁溶于 30mL 水的溶液，搅拌 60 分钟，冷却至 10℃，抽滤，水洗，干燥，得白色粉末 R（+）泮托拉唑镁 35.6g，收率：90%。

实施例 9

S（-）泮托拉唑钙（VII）的合成

将 4.23g（10mmol）的 S（-）泮托拉唑钠一水合物溶于 150mL 水中，搅拌下加入 0.56g（5mmol）氯化钙溶于 5mL 水的溶液，搅拌 60 分钟，冷却至 10℃，抽滤，水洗至滤液中无氯离子，干燥，得白色粉末 S（-）泮托拉唑钙 3.6g，收率：85%。

实施例 10

R（+）泮托拉唑钙（VIII）的合成

将 4.23g（10mmol）的 R（+）泮托拉唑钠一水合物溶于 150mL 水中，搅拌下加入 0.56g（5mmol）氯化钙溶于 5mL 水的溶液，搅拌 60 分钟，冷却至 10℃，抽滤，水洗至滤液中无氯离子，干燥，得白色粉末 R（+）泮托拉唑钙 3.4g，收率：81%。

实施例 11

S（-）泮托拉唑锌（IX）的合成

将 2.1g（5mmol）的 S（-）泮托拉唑钠一水合物溶于 150mL 水中，搅拌下加入 0.62g（5mmol）醋酸锌溶于 5mL 水的溶液，搅拌 60 分钟，冷却至 10℃，抽滤，水洗，干燥，得白色粉末 S（-）泮托拉唑锌 2.1g，收率：90%。

实施例 12

S（-）泮托拉唑或R（+）泮托拉唑分别与氢氧化钠、甲醇钠、乙醇那钠和异丙醇钠反应得到S（-）泮托拉唑钠（III）或R（+）泮托拉唑钠（IV），反应溶剂为水、丙酮、甲醇、乙醇、异丙醇，反应温度为0℃至溶剂沸点，优选20~40℃。

4. 一种如权利要求1所述的手性泮托拉唑盐的制备方法，其特征在于：

a）S（-）泮托拉唑或R（+）泮托拉唑分别与低级的醇镁如甲醇镁、乙醇镁等反应得到的S（-）泮托拉唑镁（V）或R（+）泮托拉唑镁（VI），溶剂为甲醇、乙醇、异丙醇、丙酮，反应温度为0℃至溶剂沸点，优选20~40℃。

b）S（-）泮托拉唑钾（I）和S（-）泮托拉唑钠（III）或R（+）泮托拉唑钾（II）和R（+）泮托拉唑钠（IV）同氯化镁、硫酸镁和乙酸镁等镁源反应得到S（-）泮托拉唑镁（V）或R（+）泮托拉唑镁（VI），反应溶剂为水、甲醇、乙醇、异丙醇，反应温度为0℃至溶剂沸点，优选20~40℃。

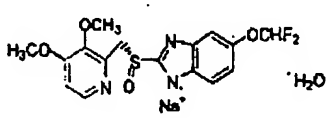
5. 一种如权利要求1所述的手性泮托拉唑盐的制备方法，其特征在于：S（-）泮托拉唑钾（I）和S（-）泮托拉唑钠（III）或R（+）泮托拉唑钾（II）和R（+）泮托拉唑钠（IV）同氯化钙、乙酸钙等钙源反应得到S（-）泮托拉唑钙（VII）和R（+）泮托拉唑钙（VIII），反应溶剂为水、甲醇、乙醇、异丙醇、丙酮，反应温度为0℃至溶剂沸点，优选20~40℃。

6. 一种如权利要求1所述的手性泮托拉唑盐的制备方法，其特征在于：S（-）泮托拉唑钾（I）和S（-）泮托拉唑钠（III）或R（+）泮托拉唑钾（II）和R（+）泮托拉唑钠（IV）同氯化锌、乙酸锌等锌源反应得到S（-）泮托拉唑锌（IX）和R（+）泮托拉唑锌（X），反应溶剂为水、甲醇、乙醇、异丙醇、丙酮，反应温度为0℃至溶剂沸点，优选20~40℃。

7. 权利要求2、3、4中所述的手性泮托拉唑盐，其特征在于：其制备过程中的S（-）泮托拉唑和R（+）泮托拉唑一种新制备方法，该方法以氯仿或乙腈为溶剂；

8. 一种如权利要求1所述的手性泮托拉唑盐，其特征在于：可与其它临床上可接受的药物组合，用于制备治疗胃溃疡、十二指肠溃疡、反流性食管炎和佐-艾氏综合症疾病的药物。

说　明　书



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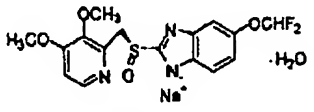
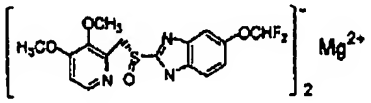


IV

S（-）泮托拉唑或R（+）泮托拉唑分别与低级的醇镁如甲醇镁、乙醇镁等反应得到的S（-）泮托拉唑镁（V）或R（+）泮托拉唑镁（VI），或S（-）泮托拉唑钾（I）和S（-）泮托拉唑钠（III）或R（+）泮托拉唑钾（II）和R（+）泮托拉唑钠（IV）同氯化镁、硫酸镁和乙酸镁等镁源反应得到S（-）泮托拉唑镁（V）或R（+）泮托拉唑镁（VI）：



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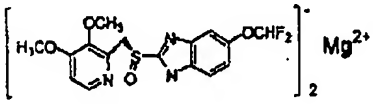
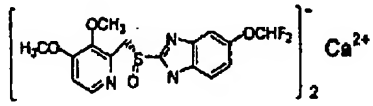
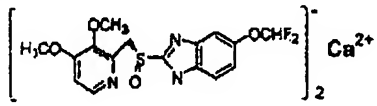


VI

S（-）泮托拉唑钾（I）和S（-）泮托拉唑钠（III）或R（+）泮托拉唑钾（II）和R（+）泮托拉唑钠（IV）同氯化钙、乙酸钙等钙源反应得到S（-）泮托拉唑钙（VII）和R（+）泮托拉唑钙（VIII）：

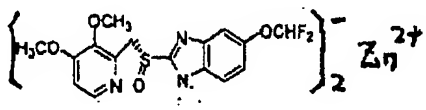


VII

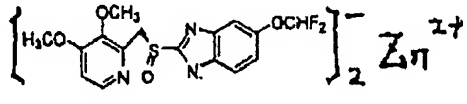


VIII

S（-）泮托拉唑钾（I）和S（-）泮托拉唑钠（III）或R（+）泮托拉唑钾（II）和R（+）泮托拉唑钠（IV）同氯化锌、乙酸锌等锌源反应得到S（-）泮托拉唑锌（IX）和R（+）泮托拉唑锌（X）。



IX



X

反应溶剂为水、甲醇、乙醇、异丙醇、丙酮，反应温度为0℃至溶剂沸点，优选20~40℃。

本发明的优点是：本发明提供了新的泮托拉唑盐的结构，可作为质子泵抑制剂，用于治疗与胃酸分泌紊乱有关的疾病，可望开发出临床上可接受的新的药物组合。本发明制备工艺方法比较简单，易行，适应工业化生产。

具体实施方式：

实施例1

S（-）泮托拉唑钾（I）的合成

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